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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,430	02/17/2000	Lawrence R. Green	15542-002310	6441

7590 12/10/2002

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	23

DATE MAILED: 12/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,430	GREEN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-45* is/are pending in the application.

4a) Of the above claim(s) *23-27,36-38 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,28-35,39 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 22 (filed 10/10/02), claim 18 has been amended, and claims 43-45 added. Claims 18-45 are pending; claims 23-27, 36-38, 40-42 remain withdrawn from consideration. Claims 18-22, 28-35, 39, 43-45 are examined in this Office action.

Applicants' arguments filed 10/10/02 have been considered and found not persuasive

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Claim 18 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,096,713. Although the conflicting claims are not identical, they are not patentably distinct from each other.

> The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d)

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 19, 21, 22, 28-35, 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is lacking for the claimed method for cases in which R", taken together with the carboxyl group of tryptophan, represents an amide.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, inhibition of neovascularization is unpredictable when R", taken together with the carboxyl group of tryptophan, represents an amide. For example, Cameron N. E. (*Diabetologia* **35** (1) 12-8, 1992) examined the effects of lisinopril on slow and fast twitch muscle contractile properties nerve conduction and hypoxic resistance, and muscle and nerve capillary density in streptozotocin-diabetic rats. One of the findings was that in streptozotocin-diabetic rats, an increase in the capillary/fiber ratio occurred in extensor digitorum longus muscles, and that this particular finding was consistent with the possibility that lisinopril promoted angiogenesis in this particular situation. Thus, if the capillary/ fiber ratio increases in extensor digitorum longus muscles that are present in streptozotocin-diabetic rats, it follows therefrom that ACE inhibitors generally will promote

neovascularization, rather than inhibit it. When R", taken together with the carboxyl group of tryptophan, represents an amide, ACE inhibitors are encompassed. For example, Haber [*Prog. Biochem. Pharmacol.* (1976), **12** (Drugs Affecting Renin-Angiotensin- Aldosterone Syst., Proc. Kanematsu Conf. Kidney, 5th), 16-32] discloses that the peptide EWPRFQIPP is an ACE inhibitor. Thus, when R", taken together with the carboxyl group of tryptophan, represents an amide, success at inhibition of neovascularization becomes "unpredictable". It is suggested that the claims be amended to eliminate the possibility that R", taken together with the carboxyl group of tryptophan, can represent an amide.

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Claims 18-22, 28-35, 39, 43-45 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In each of claims 18 and 19, the phrase "less than about" is used. This renders indefinite as to the upper limit of the molecular weight. It is suggested that "about" be deleted. If deemed appropriate, a second claim could be added which includes the phrase "about 5000 Daltons", or "about 1000 Daltons", but which claim does not also include the phrase "less than".

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness

rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 18, 19, 21, 22, 28-35, 39, are rejected under 35 U.S.C. §103 as being unpatentable over Haber [*Prog. Biochem. Pharmacol.* (1976), **12** (Drugs Affecting Renin-Angiotensin-Aldosterone Syst., Proc. Kanematsu Conf. Kidney, 5th), 16-32] in view of Rodgers (USP 5,716,935).

As indicated previously, Haber discloses (e.g., page 17) that the peptide EWPRFQIPP inhibits the enzyme ACE. Haver does not disclose that inhibitors of ACE are also effective to inhibit neovascularization or angiogenesis. Rodgers discloses (col 3, line 5-10) that angiotensin stimulates neovascularization and angiogenesis. Rodgers does not disclose any of the peptides that are encompassed by the instant claims.

Applicants have responded by arguing that, unless the biochemist of ordinary skill perceived inhibition of neovascularization to be a desirable outcome, he would believe that

such an outcome is impossible, or at least unlikely. However, biochemical systems do not "know" whether people perceive them to be desirable or undesirable. By way of example, if one reference were to disclose that all mammals are warm-blooded, and a second reference were to disclose that all dogs are mammals, would the conclusion that all dogs are warm-blooded be any less obvious if there existed people who wished that it weren't true? In the instant case, the biochemist of ordinary skill need have no opinion as to the desirability of inhibiting neovascularization; the biochemist, in possession of the references, would have viewed it as inevitable, or at least likely.

Next, applicants have imposed what amounts to an "enablement" rejection of the examiner's §103 rejection. Applicants have pointed to Cameron N. E. (*Diabetologia* **35** (1) 12-8, 1992). In this reference, the effects of lisinopril on slow and fast twitch muscle contractile properties nerve conduction and hypoxic resistance, and muscle and nerve capillary density were examined in streptozotocin-diabetic rats. One of the findings was that in streptozotocin-diabetic rats, an increase in the capillary/fiber ratio occurred in extensor digitorum longus muscles, and that this particular finding was consistent with the possibility that lisinopril promoted angiogenesis in this particular situation. Perhaps it is true that in humans who are diabetic, a similar increase in the capillary/fiber ratio occurred in extensor digitorum longus muscles (assuming humans even have such muscles). But this ground of rejection is based on the supposition that the subject is not diabetic. Certainly

the majority of humans are not diabetic, and laboratory animals are certainly not diabetic unless the researcher makes the deliberate decision to induce such a state. Accordingly, for non-diabetic animals, the claims remain obvious. Moreover, there is at least one reference which "neutralizes" applicants argument. Fujita Mamoru (*Biochemical and Biophysical Research Communications* 294 (2) 441-7, 2002) endeavored to determine the propensity of lisinopril to inhibit angiogenesis, and found lisinipril to be effective in this regard. Moreover, the results were more definitively stated than in Cameron, and was undertaken on test animals which were not diabetic.

The rejection is maintained.

*

Claims 18, 19, 21, 22, 28-35, 39, are rejected under 35 U.S.C. §103 as being unpatentable over Haber [*Prog. Biochem. Pharmacol.* (1976), **12** (Drugs Affecting Renin-Angiotensin-Aldosterone Syst., Proc. Kanematsu Conf. Kidney, 5th), 16-32] in view of Rodgers (USP 5,716,935) further in view of Folkman (*J Natl Cancer Inst* **82**, 4-6, 1990)

The teachings of Haber and of Rodgers were indicated previously. Neither reference discloses that inhibition of neovascularization is "desirable". Folkman discloses that inhibition of neovascularization is "desirable". Folkman does not disclose any of the compounds underlying the instant method claims.

When the §103 rejection was imposed over Haber in view of Rodgers, applicants argued

that the probability of success was determined not so much by biochemical factors as by the opinion of the biochemist as to what might be desirable. As indicated, this "deficiency" is now remedied by Folkman.

Thus, the claims are rendered obvious.

*

It is suggested that claims 23-24 be amended to recite that the subject is afflicted with one of the indicated conditions. Currently, the phrase "the condition" lacks antecedent basis.

Reference "AT" (Maione, 1995) was not considered because it is not legible.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800